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Metabolic Polymoryphisms, Smoking, and Oral Cancer in Puerto Rico

Heng Xie,* Lifang Hou,† Peter G. Shields,¶ Deborah M. Winn,‡
Gloria Gridley,† Eleuterio Bravo-Otero,# Scott R. Diehl,** Elise D. Bowman,§
Linda M. Brown,† and Richard B. Hayes†[1]

*Division of Cancer Treatment and Diagnosis, †Division of Cancer Epidemiology and Genetics,
‡Division of Cancer Control and Population Sciences, and §Laboratory of Human Carcinogenesis,
National Cancer Institute, Bethesda, MD 20892
¶Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC 20007
#School of Dentistry, University of Puerto Rico, San Juan, PR 00936-5067
**Center for Pharmacogenomics and Complex Disease Research, New Jersey Dental School,
UMDNJ, Newark, NJ 07101-1709

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Genetic polymorphisms resulting in variation in metabolism of tobacco carcinogens may influence oral cancer risk. In a population-based case–control study in Puerto Rico, genotypes of *CYP1A1*, *GSTM1*, and *GSTT1* were determined by a PCR-based method for 132 oral cancer patients and 143 control subjects. Genotype-associated risks were estimated by logistic regression. The null variant of *GSTM1* was associated with a marginally significant decrease in oral cancer risk [odds ratio (OR) = 0.6, 95% confidence interval (CI) = 0.3–1.0, and *P* for trend = 0.09]. Risks increased with increasing cigarette use among subjects with the *GSTM1*-present genotype (*P* for trend <0.0001), rising to OR = 9.5, 95% CI = 3.0–30, among the heaviest cigarette users. In contrast, among subjects with the *GSTM1*-null genotype, risks did not clearly increase with increasing cigarette use (*P* for trend <0.61; OR = 1.8, 95% CI = 0.6–5.2 among the heaviest tobacco users). The *GSTT1*-null variant (OR = 1.0, 95% CI = 0.5–1.9) and $CYP1A1^{462Val}$ variant (OR = 0.9, 95% CI = 0.5–1.7) were not associated with the risk. Risks rose with increasing cigarette use in a similar manner for subjects with or without the $CYP1A1^{462Val}$ variant (*P* for interaction = 0.3) and for subjects with or without the *GSTT1*-null genotype (*P* for interaction = 0.4). In conclusion, cigarette use significantly increased the risk of oral cancer in this population. The *GSTM1*-present genotype was associated with higher tobacco-associated risk for oral cancer among heavy smokers than the null genotype.

Key words: Polymorphism; Enzymes; Smoking; Carcinoma

The incidence of oral cavity and pharyngeal cancers (referred to here after as oral cancer) among Puerto Rican men is among the highest in the Western hemisphere (1,2). As found in other epidemiologic studies (3), cigarette smoking and alcohol use are major risk factors for oral cancer in this population (4). Many chemical carcinogens found in tobacco smoke, including polycyclic aromatic hydrocarbons (PAHs[2]) and benzo[*a*]pyrene (BaP), undergo metabolic activation by phase I enzymes (e.g., P450 system) and detoxification by phase II enzymes (e.g., glutathione-*S*-transferases) prior to excretion (5,6). The *CYP1A1* gene encodes for aryl hydrocarbon hydroxylase, a major phase I enzyme involved in the metabolism of PAH (7,8). A polymorphic change from Ile to Val at amino acid position 462 of *CYP1A1* ($CYP1A1^{462Val}$) has been reported to modulate risk for smoking-related diseases, including oral and lung cancer (7,9,10).

GSTM1 and GSTT1 are glutathione-*S*-transferase isoenzymes catalyzing conjugation and subsequent elimination of carcinogens such as BaP in tobacco smoke (11, 12). Carriers of homozygous gene deletions in *GSTM1* or *GSTT1* have an absence of GST-μ or GST-θ enzyme activity, respectively, with a subsequent loss of metabolizing capacity of both potential carcinogens and chemopreventive agents (13–16).

Genetic polymorphisms of these phase I and phase II metabolic enzymes have been implicated as a possible mechanism that may underlie the differential risk for oral cancer among cigarette users with similar smoking exposures (17). In this study, we evaluated whether the

[1]Address correspondence to Richard B. Hayes, D.D.S., Ph.D., Division of Cancer Epidemiology and Genetics, National Cancer Institute, Executive Plaza South, Rm. 8114, 6120 Executive Blvd., Bethesda, MD 20892-7240. Tel: (301) 496-9093; Fax: (301) 402-1819; E-mail: hayesr@mail.nih.gov
[2]Abbreviations used: Abbreviation: PAH, polycyclic aromatic hydrocarbon; BaP, benzo[*a*]pyrene.

genetic polymorphisms of *CYP1A1, GSTM1*, and *GSTT1* modify the risk of smoking-related oral cancer.

MATERIALS AND METHODS

Study Subjects

Study subjects were part of a population-based, case–control study conducted in Puerto Rico to investigate risk factors for oral cancer (2,4). A detailed description of the study design and methods is provided elsewhere (2). Briefly, 299 cases, identified through the Puerto Rico Central Cancer Registry and island pathology laboratories, and 258 controls were eligible to provide oral epithelial cell specimens for genetic studies. Eligible case and control subjects included those residing in the San Juan metropolitan area and those residing elsewhere on the island who were interviewed after June 28, 1994. Subjects residing outside the San Juan metropolitan area who were interviewed on or before June 28, 1994 were not eligible for donation of oral epithelial cell specimens. Buccal cell collection for genetic studies was successfully obtained from 157 (53%) cases and 149 (58%) controls. Salivary gland cancer patients ($n = 9$) as well as 16 cases and 6 controls with undetermined *CYP1A1, GSTM1*, and *GSTT1* genotypes were excluded from our study. The final study group for the present analysis included 132 cases and 143 controls. All subjects gave written informed consent to participate in the study, following institutional review board approvals at the National Cancer Institute and the University of Puerto Rico.

Demographic Information and Cancer Risk Factors

Trained interviewers used a structured questionnaire in Spanish to collect information from the participants, including selected demographic factors, usual diet, and history of tobacco and alcohol use. Detailed information was collected on tobacco use (including tobacco type, age started, age stopped, total years, and amount usually used). Ever smokers were persons who had smoked at least 100 cigarettes in their lifetime. Persons were considered to have used cigars, pipe, snuff, or chewing tobacco when these products were used for 6 months or more. Never smokers were those who never smoked, smoked less than 100 cigarettes, or used other tobacco products for less than 6 months. Among 33 cigars and pipe users, 27 subjects also smoked at least 100 cigarettes in their lifetime and were considered as cigarette smokers in the analysis. Six subjects were cigar and pipe only users, and were excluded from the analysis. Lifetime consumption of cigarettes was estimated from usual daily consumption of cigarettes and total years of use. Pack-years of cigarette use (packs/day × years) and lifetime number of drinks were computed from the interview data. Based on controls, tertiles were used in grouping age (<66, 66–71 and >71 years), lifetime cigarette consumption (<8.5, 8.5–36, and >36 pack/year) among cigarette smokers, lifetime alcohol consumption (<9648, 9648–42,000, and >42,000 drinks) among alcohol drinkers, and raw vegetable and fruit intake (<3.13, 3.13–5 and >5 servings per day).

Collection of Oral Epithelial Cell Specimens

Oral epithelial cells were collected by brushing the buccal mucosa with a soft-bristled cytobrush (Medical Packaging Corp., Camarillo, CA), rinsing the mouth with 10 ml sterile water, mixing the rinse expectorate with 10 ml 2× standard transport medium (STM) (Digene Diagnostics, Inc., Silver Spring, MD), and then storing at −70°C (18).

Genotype Analysis

Procedures for genomic DNA extraction are described elsewhere (2). DNA (100 ng) from buccal cells was amplified by a PCR-based method, using three simultaneous sets of primers for *CYP1A1, GSTM1*, and *GSTT1* (19,20). Successful amplification was determined on a 2.2% agarose gel by the presence of a 332-bp band for the *CYP1A1* (which also served as a positive control for the null genotypes of *GSTM1* and *GSTT1*), a 273-bp band for the *GSTM1*, and a 480-bp band for the *GSTT1*. PCR products were subjected to simultaneous *Hin*fI and *Nco*I digests (New England Biolabs, Beverly, MA). When electrophoresised on a 4% NuSieve 3:1 agarose gel (FMC, Rockland, ME), the *CYP1A1* Val/Val allele was indicated by bands at 263 and 69 bp, the *CYP1A1* Ile/Ile allele resulted in bands at 232, 69, and 31 bp, and the *GSTM1* yielded multiple bands at 154, 46, 44, and 29 bp. The absence of either a *GSTM1*- or a *GSTT1*-specific fragment indicated the corresponding null genotype, confirmed by the appearance of a positive control band. In addition, parallel quality control assays were carried out and validated each time by confirming polymorphic Mendelian inheritance patterns with commercially known standard DNA samples from NIGMS Human Genetic Mutant Cell Repository (Coriell Institute, Camden, NJ) (data not shown).

Statistical Analysis

Associations between cigarette use and oral cancer were assessed by computing the odds ratio (OR) and 95% confidence interval (CI), using logistic regression analysis. In all statistical models, we adjusted for age, gender, and, where indicated, lifetime alcohol consumption and raw vegetable and fruit intake, using categorical variables based on the Hosmer-Lemeshow goodness-of-fit test.

Tests for interactions (on the multiplicative scale) between cigarette use and each genotype, and between genotypes, were carried out by the likelihood ratio test, comparing a "reduced" model including main effect terms versus a "full" model containing main effects and the respective interaction terms for the respective parameters. All tests of statistical significance were two-sided. The Stata statistical package was used for all analyses (Stata Corporation, College Station, TX; release 7.0).

RESULTS

Consistent with our previous report for the entire case–control group, cases of oral cancer had greater alcohol consumption than controls (4). Cases also reported lower consumption of raw fruits and vegetables (Table 1).

Use of cigarettes was associated with an increased risk for oral cancer (OR = 2.1, 95% CI = 1.0–4.2). Risk increased with increasing pack-years ($P_{trend} < 0.0001$), reaching OR = 4.8, 95% CI = 2.1–11.0 in the highest use category. The *GSTM1*-null genotype was associated with a reduced risk for oral cancer (OR = 0.6, 95% CI = 0.3–1.0), while no association was found with the *GSTT1*-null genotype (OR = 1.0, 95% CI = 0.5–1.9) (Table 2). Because the *CYP1A1* Val/Val genotype was rare, we compared the Ile/Ile genotype with the combined group of subjects with Ile/Val and Val/Val genotypes. No association was found with oral cancer for the combined group (OR = 0.9, 95% CI = 0.5–1.7) or with Ile/Val and Val/Val group separately (data not shown). We did not observe significantly increased risks and interactive relationships when the combination of paired genotypes of these three genes (i.e., *GSTM1–GSTT1*, *GSTM1–CYP1A1*, and *GSTT1–CYP1A1*) were evaluated in the analysis (data not shown).

Risks associated with ever use of cigarettes were greater for subjects with *GSTM1* present (OR = 2.1, 95% CI = 0.9–5.3) than for those who were null for the allele (OR = 1.2, 95% CI = 0.5–3.1). Among those with *GSTM1* present, risks rose with increasing cigarette use to OR = 9.5 (95% CI = 3.0–30) for those who had greater than 36 pack-years of lifetime consumption ($P_{trend} < 0.0001$). Among those who were null for the *GSTM1* allele, OR = 1.8 among the heaviest users; however, there was no significant evidence of a dose–response trend ($P_{trend} < 0.61$). Interactions were not observed between *GSTM1* and ever use ($P = 0.81$); however, a modest interaction was observed with pack-years ($P = 0.06$) of cigarettes and *GSTM1* genotype.

Cigarette-associated oral cancer risks were similar for subjects with the functional or the null genotypes for *GSTT1* (OR = 2.0, 95% CI = 0.9–4.5 vs. OR = 2.1, 95% CI = 0.8–5.8) (Table 3), as were the significant trends in risk with increasing cigarette use. Similarly, no clear interrelationships were noted between the *CYP1A1* genotypes, cigarette use, and oral cancer risk.

Table 1. Distribution of Demographic Factors, Alcohol Use, and Raw Fruits and Vegetable Intake Among Cases and Controls

Characteristics	Cases (%) ($n = 132$)	Controls (%) ($n = 143$)
Gender		
Male	119 (90.1)	110 (76.9)
Female	13 (9.9)	33 (23.1)
Age (years)		
<66	69 (52.2)	51 (35.6)
66–71	34 (25.8)	45 (31.5)
>71	29 (22.0)	47 (32.9)
Race		
White	88 (66.7)	100 (69.9)
Black	14 (10.6)	10 (7.0)
Mestizo	19 (14.4)	23 (16.1)
Other	11 (8.3)	10 (7.0)
Lifetime alcohol consumption (drinks)		
Never	11 (8.3)	40 (27.9)
<9648	10 (7.6)	34 (23.8)
9648–42,000	19 (14.4)	34 (23.8)
>42,000	92 (69.7)	35 (24.5)
Raw vegetables & fruits (servings per day)		
<3.13	77 (58.3)	47 (32.9)
3.13–5	33 (25.0)	48 (33.6)
>5	22 (16.7)	48 (33.5)

DISCUSSION

In our population-based case–control study, the null *GSTM1* genotype was associated with reduced risk for oral cancer. A strong dose–response for oral cancer was observed with increasing cigarette use among *GSTM1*-present but not among *GSTM1*-null individuals, further indicating that enzyme deficiency does not increase tobacco-associated risk. No evidence was found that *GSTT1* or *CYP1A1* polymorphisms were related to oral cancer risk.

GSTM1 conjugates a variety of electrophilic compounds, including carcinogens and cytotoxic drugs. The defective enzyme associated with the *GSTM1*-null genotype is generally considered a potential risk factor for cancer (15,21–23), including oral cancer (24–27). Our study showing reduced risks with the *GSTM1*-null genotype and results from several investigations showing no association with *GSTM1* (28–31) diminish the likelihood that defective GSTM1 enzyme increases oral cancer risk.

Table 2. Risk of Oral Cancer by Smoking and Genetic Polymorphisms in *GSTM1, GSTT1*, and *CYP1A1* Genes

	Cases (%) (n = 132)	Controls (%) (n = 143)	OR	95% CI
Cigarette use				
Never	20 (15.2)	63 (44.1)	1.0	
Ever (pack-years*)	112 (84.8)	80 (55.9)	2.1	1.0–4.2
<8.5	6 (4.6)	28 (19.6)	0.5	0.2–1.6
8.5–36	29 (22.1)	25 (17.5)	2.0	0.8–4.9
>36	77 (58.3)	27 (18.9)	4.8	2.1–11.0
			$P_{trend} < 0.0001$	
GSTM1				
Present	83 (62.9)	78 (54.6)	1.0	
Null	49 (37.1)	65 (45.4)	0.6	0.3–1.0
GSTT1				
Present	93 (70.5)	101 (70.6)	1.0	
Null	39 (29.5)	42 (29.4)	1.0	0.5–1.9
CYP1A1				
Ile/Ile	89 (67.5)	92 (64.3)	1.0	
Ile/Val	39 (29.5)	43 (30.1)		
Ile/Val & Val/Val	4 (3.0)	8 (5.6)	0.9	0.5–1.7

OR: odds ratio (adjusted for sex, age, lifetime alcohol consumption, and raw vegetable and fruit intake). CI: confidence interval.
*pack-years = packs/day × years.
†$P_{trend} < 0.0001$.

The effects of glutathione-dependent chemical carcinogen detoxification may be related in subtle ways to chemical exposure patterns, with some investigations indicating that genotype-associated risks are dependent upon the level of exposure to tobacco smoke (24). Our dose–response evaluation indicated that high dose of cigarette use increased oral cancer risk among *GSTM1*-present genotype carriers, contrasting with other studies (24,25); the underlying reasons for these differences are unclear.

The *GSTT1*-null genotype was shown to increase the risk for oral and pharyngeal cancers in a previous study on French smokers (26), but most other investigations (27,28,31), including ours, did not find an association with risk of oral cancer. In addition, in our study, the *GSTT1*-null genotype did not modify the risk of oral cancer conferred by cigarette smoking.

Smokers who carried $CYP1A1^{462Val}$ polymorphism exhibited greater prevalence of PAH–DNA adducts in peripheral white blood cells (32), and are reported to have higher risks for several tobacco-related cancers (7,9,10). Several studies have demonstrated an increased oral cancer risk among the $CYP1A1^{462Val}$ polymorphism carriers, including one study showing an excess risk among low-use cigarette smokers (29,33,34). In contrast, the present study, similar to other studies in Caucasians (35–37), showed no effect of the $CYP1A1^{462Val}$ polymorphism on risk for oral cancer.

Because the function of *GSTM1, GSTT1*, and *CYP1A1* genes is closely related, previous studies have investigated the possible role of the combinations of their polymorphisms. A few studies have demonstrated increased risks among subjects who had the combination of *GSTM1*- and *GSTT1*-null genotypes and three studies have shown an increased risk among individuals who had both $CYP1A1^{462Val}$ and *GSTM1*-null genotypes (28). However, in our study, as also seen in other studies (28, 38), no significant increased risk was observed among subjects carrying two null genotypes in *GST* genes, or one null genotype in either of *GST* genes and the $CYP1A1^{462Val}$ polymorphism. Inconsistencies between the results of the different studies could be due to variations in the levels of exposure to GSTM1, GSTT1, and CYP1A1 substrates, such as BaP, across study populations.

Our study was population based, while most other previous studies were hospital based (28). We are thus more confident that the prevalence of polymorphic variants among controls in our investigation reasonably represents the true prevalence in the study population. However, our study is relatively small, which hindered us from conducting gene–gene interaction analyses by cigarette use. The study had sufficient power to detect twofold risks (two-sided) associated with polymorphic variants in *GSTM1, GSTT1*, and *CYP1A1* genes, but we cannot rule out false-negative results for more modest risks.

Table 3. Risk of Oral Cancer by Joint Effects of Smoking With Genetic Polymorphisms in *GSTM1, GSTT1*, and *CYP1A1* Genes

	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	*P* Value Interaction
		GSTM1 (present)				*GSTM1* (null)			
Cigarette use									
Never	12	34	1.0		8	29	0.6	0.2–2.0	
Ever (pack-years*)	71	44	2.1	0.9–5.3	41	36	1.2	0.5–3.1	$P = 0.81$
<8.5	3	20	0.4	0.1–1.6	3	8	0.7	0.1–3.4	
8.5–36	14	15	1.6	0.5–5.0	15	10	1.9	0.5–6.9	
>36	54	9	9.5	3.0–30	23	18	1.8	0.6–5.2	
			$P_{trend} < 0.0001$				$P_{trend} = 0.6$		$P = 0.06$
		GSTT1 (present)				*GSTT1* (null)			
Cigarette use									
Never	14	40	1.0		6	23	0.9	0.3–3.0	
Ever (pack-years*)	79	61	2.0	0.9–4.5	33	19	2.1	0.8–5.8	$P = 0.85$
<8.5	5	25	0.5	0.1–1.6	1	3	0.9	0.1–10.5	
8.5–36	18	13	2.6	0.9–7.9	11	12	1.3	0.4–4.2	
>36	56	3	4.1	1.6–10.3	21	4	7.7	1.9–30.8	
			$P_{trend} = 0.0003$				$P_{trend} = 0.0002$		$P = 0.4$
		CYP1A1 (Ile/Ile)				*CYP1A1* (Ile/Val & Val/Val)			
Cigarette use									
Never	12	39	1.0		8	24	1.3	0.4–4.1	
Ever (pack-years*)	77	53	2.4	1.0–5.8	35	27	1.9	0.8–4.9	$P = 0.52$
>8.5	2	15	0.4	0.1–2.2	4	13	0.7	0.2–2.8	
8.5–36	18	20	1.6	0.5–4.7	11	5	4.0	1.0–15.9	
>36	57	18	6.3	2.3–16.8	20	9	3.3	1.0–10.8	
			$P_{trend} < 0.0001$				$P_{trend} = 0.13$		$P = 0.3$

OR: odds ratio (adjusted for sex, age, lifetime alcohol consumption and raw vegetable and fruit intake). CI: confidence interval.
*pack-years = packs/day × years.

In conclusion, cigarette use significantly increased the risk of oral cancer in this Puerto Rico population. The *GSTM1*-present genotype was associated with higher tobacco-associated risk for oral cancer among heavy smokers than the null genotype.

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